Risk factors of synchronous peritoneal metastases in colorectal cancer: a meta-analysis

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Research article

Keywords: Colorectal cancer, Synchronous peritoneal metastases, Risk factors, Meta-analysis

Posted Date: April 12th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-390534/v1

Abstract

Background: Early detection of synchronous colorectal peritoneal metastasis (CPM) is difficult due to the absence of typical symptoms and the low accuracy of imaging examinations. Better knowledge of risk factors for synchronous CPM may be essential for early diagnosis and strengthening management. This study aimed to clarify the risk factors.

Methods: This meta-analysis was based on PRISMA guidelines. A systematic search of PubMed, Embase and Cochrane Library databases was performed. The pooled data was assessed by a random-effects model.

Results: 25 studies containing 171932 patients were included. Synchronous CPM was associated positively with female (OR 1.299; 1.118 to 1.509; P = 0.001), T4 (OR 12.331; 7.734 to 19.660; P < 0.001), N1-2 (OR 5.665; 3.628 to 8.848; P < 0.001), poorly differentiated grade (OR 2.560; 1.537 to 4.265; P < 0.001), right-sided colon cancer (OR 2.468; 2.050 to 2.970; P < 0.001), mucinous adenocarcinoma (OR 3.565; 2.095 to 6.064; P < 0.001), signet-ring cell carcinoma (OR 4.480; 1.836 to 10.933; P = 0.001), elevated serum CA19-9 (OR 12.868; 5.196 to 31.867; P < 0.001), PROK1/PROKR2-positive (OR 2.244; 1.031 to 4.884; P = 0.042) and BRAF mutations (OR 2.586; 1.674 to 3.994; P < 0.001). However, it's associated negatively with rectal cancer and non-mucinous adenocarcinoma, and not associated with KRAS, NRAS, PIK3CA mutations and MSI-H/dMMR.

Conclusions: These risk factors are the alerts that could predict the presence of synchronous CPM and contribute to strengthening management and optimal therapeutic strategy.

Background

Colorectal cancer (CRC) has become the third most common malignant tumors, with the second highest mortality worldwide[1]. Of all CRC, 8.3-15 percent have peritoneal metastases (PM)[2-4]. Up to 4.3-7.8 percent of CRC present with synchronous PM[2, 5-7]. PM is a well-known negative prognostic factor. Several recent large studies have shown substantially shorter survival with peritoneal metastasis of colorectal cancer (pmCRC) than metastases at other sites[8-10]. For example, the overall survival of pmCRC patients was 12.7 versus 17.6 months for metastases at other sites, with a significant p-value (p < 0.001)[9]. Therefore, this special type of metastatic disease of CRC deserves more attention.

Early detection of synchronous CPM is currently difficult due to the absence of typical symptoms and the low accuracy of non-invasive imaging examinations in nodules smaller than 5 mm[11-13]. In fact, a considerable proportion of synchronous CPM are unexpectedly detected during primary surgery[14]. Consequently, if that is the case, the extent of disease can only be evaluated during surgery, and treatment strategies are often selected at this time, which may determine a suboptimal treatment approach. Many hospitals are still lack of equipment for HIPEC nowadays. In addition, the concept and surgical proficiency of cytoreduction surgery may vary among different surgeons[5]. These may be unfavorable to the therapeutic strategies for CPM diagnosed during operation. Better knowledge of risk

factors for synchronous CPM would increase the level of suspicion in patients with no suggestive signs or symptoms, and thus allow physicians to treat these patients more adequately, such as more aggressive preoperative examination, proactive laparoscopic exploration or referring them to specialized centers.

Several studies have tried to determine the risk factors of synchronous CPM, but with heterogeneous outcomes, such as the location of primary tumor[8, 15], MSI-H[16-18]. Furthermore, many studies only focused on the aspect of clinicopathological characteristics of synchronous CPM, and thus they were lack of systematic and comprehensive analysis of molecular characteristics.

Further comprehensive understanding of its clinicopathological and molecular features may be necessary for early diagnosis and may help to enhance the management of patients at high risk of synchronous CPM. Therefore, a systematic review and meta-analysis of all studies comparing gender, tumor invasion depth, lymph node metastasis, differentiation, location of primary tumor, histology, serum CA19-9, PROK1/PROKR2, BRAF, KRAS, NRAS, PIK3CA and MSI-H/dMMR status between synchronous pmCRC and non-pmCRC was undertaken.

Methods

This systematic review and meta-analysis adhered to the recommendations of the Preferred Reporting Items of Systematic Reviews and Meta-analysis (PRISMA) statement[19]. PRISMA Checklist is available in supplementary **Appendix 1**.

Study registration

This study was registered at PROSPERO (Prospective Register of Systematic Reviews, www.crd.york.ac.uk/prospero). Number CRD42020198548.

Eligibility criteria

Colorectal peritoneal metastases can be divided into synchronous CPM and metachronous CPM. Synchronous CPM has different definitions[5, 6, 20]. Referring to the international consensus on colorectal liver metastases[21], synchronous CPM is defined as peritoneal metastases detected at or before diagnosis or surgery of the primary CRC; metachronous CPM is defined as those detected after curative surgery.

Comparative studies of primary colorectal tumor with or without synchronous PM involving data on clinicopathological and molecular characteristics were eligible for inclusion. The included studies need to use the recognized diagnostic criteria, as follows: the primary tumor's pathological diagnosis was confirmed; the tumor cells were primary in colorectal tumor; and the patient's synchronous PM was confirmed by imaging diagnosis before surgery, intraoperative exploration or histopathological examination.

The exclusion criteria were: (1) case reports, review articles and animal studies; (2) non-English publications; (3) studies that are not related to CRC or PM; (4) metachronous PM; (5) no analysis of the risk factors; (6) no comparator group; (7) no relevant data, including articles published only in abstract form as well as studies without complete data and inability to construct a 2×2 contingency table; (8) mixed primary tumor; (9) non-standardized histological type (10) synchronous CPM was not clearly or correctly defined.

Data sources and search strategy

We selected relevant studies by searching PubMed, Embase and the Cochrane CENTRAL Register of Controlled Trials. The following combined terms were used in the search: (peritoneal metastasis OR peritoneal metastases OR peritoneal carcinomatosis) AND (colorectal OR colon OR rectal). The latest search was implemented on 14 July 2020 and the earliest search was not limited in the relevant database.

Selection process

Two independent authors (Y.Z and X.Q) checked the title and abstract of each study, and studies that satisfied the potential eligibility were obtained for further full-text assessment. Disagreements were resolved by discussion with senior authors (Y.D or H.W) until consensus was achieved.

Data extraction

By using standardised forms, two independent authors (Y.Z and X.Q) extracted the data from each eligible study. The authors resolved disagreements by discussion with senior authors (Y.D or H.W). The following data were extracted from each eligible study: author, year of publication, country where the study was conducted, setting of centre, type of study, enrollment interval, number of primary CRC patients with or without synchronous PM, clinicopathological and molecular characteristics. In addition, the score of Newcastle–Ottawa Scale (N-O score) for eligible studies was also calculated and extracted.

Statistical analysis

We used Comprehensive Meta-Analysis (version 2.0) and Stata (version 12.0) for all statistical analyses. All pooled outcomes were determined using a random-effects model (DerSimonian-Laird method). In pooled analyses of associations between various clinicopathological-molecular factors and synchronous CPM, effect sizes were calculated as odds ratios (OR) with a 95 percent confidence interval (CI). The χ^2-based Cochran Q test was used to assess heterogeneity between studies, in which $P < 0.1$ indicates the presence of heterogeneity[22]. We also did I^2 inconsistency testing to assess the extent of the heterogeneity between studies, with values greater than 50% regarded as moderate-to-high heterogeneity[23]. For significant heterogeneity, we tried to do sensitivity analysis or subgroup analysis to find its potential sources. Sensitivity analysis was performed by omitting each study sequentially to test the influence of each individual study on the pooled result. Publication bias was evaluated by visual

inspection of the funnel plot for symmetry (an asymmetric plot suggested possible publication bias) and quantified by means of Begg's test, with P value < 0.05 regarded as significant publication bias.

The quality of included studies was assessed using the Newcastle-Ottawa Scale[24], in which a score ≥ 6 indicates the high-quality of studies. The quality of studies was evaluated by examining 3 categories: patient selection, comparability of the 2 study groups, and assessment of exposure (maximum score 9), as was shown in the Newcastle-Ottawa Scale.

Results

Search and selection results

The initial search yielded a total of 9470 studies. After removal of duplicates, a total of 7659 studies were screened by analysis of title and abstract, and 7435 studies were removed because they met one or more exclusion criteria. The leaving 224 studies were then assessed for eligibility by full-text examination, and a further 199 were excluded for ineligibility. Reasons for exclusion were recorded. Finally, 25 studies[3, 8, 15-18, 25-43] were included in the final analysis (**Fig. 1**).

Study characteristics

Among the 25 included studies, 7 had a multicentre setting and 18 had a single centre design. Five of the included studies were prospectively performed; the remaining twenty were retrospective. 22 studies were considered of high quality (N-O score ≥ 6), and 3 studies were considered of low quality. Complete characteristics of the included studies are available in **Table 1**.

Factors not included in the quantitative synthesis

Six of clinicopathological and molecular factors could not be included in quantitative synthesis because they had only a single study of their subgroup, or their methodology did not permit pooling data. The six factors were serum CEA[25], serum CA125[32], CTGF (connective tissue growth factor)[40], DDR2 (discoidindomain receptor 2)[30], VIM (vimentin)[42], and TP53[28] respectively. We included these factors in table 1 for completeness, but not in the final quantitative synthesis through meta-analysis.

Finally, 21 studies about 13 factors were included in the quantitative synthesis through meta-analysis, 7 studies on gender, 4 studies on tumor invasion depth, 3 studies on lymph node metastasis, 5 studies on differentiation, 6 studies on primary tumor site, 7 studies on histology, 2 studies on serum CA19-9, 2 studies on PROK1/PROKR2, 9 studies on BRAF, 6 studies on KRAS, 2 studies on NRAS, 2 studies on PIK3CA and 4 studies on MSI-H/dMMR status.

Gender

Seven studies[8, 15, 17, 18, 25, 33, 41], including data on 160679 patients (30366 synchronous pmCRC, 130313 non-pmCRC) regarding gender, were included for eligibility in the meta-analysis. The pooled

analysis indicated that female was associated positively with synchronous CPM compared with male (OR 1.299; 95% CI, 1.118 to 1.509; P = 0.001) (**Fig. 2a**). There was significant heterogeneity (Cochran Q, P < 0.001; I^2 = 76.9 percent). In order to explore possible sources of heterogeneity, sensibility analysis was performed by omitting each study sequentially to test the influence of each individual study on the pooled result. When one study[17] was omitted, there was no significant heterogeneity (Cochran Q, P = 0.099; I^2 = 46.0 percent), with no noticeable influence on the pooled OR and confidence interval. It's noteworthy that the rate of female in the synchronous CPM group was > 50 percent in that one study, but the others were < 50 percent.

Tumor invasion depth

Four studies[3, 15, 25, 41], including data on 19432 patients (809 synchronous pmCRC, 18623 non-pmCRC) regarding tumor invasion depth, were included for eligibility in the meta-analysis. The pooled analysis indicated that T4 was associated positively with synchronous CPM compared with T1-3 (OR 12.331; 95% CI, 7.734 to 19.660; P < 0.001) (**Fig. 2b**). There was significant heterogeneity (Cochran Q, P = 0.009; I^2 = 74.2 percent). When one study[41] was omitted through sensibility analysis, there was no significant heterogeneity (Cochran Q, P = 0.593; I^2 = 0 percent), with no noticeable influence on the pooled result.

Lymph node metastasis

Three studies[3, 15, 41], including data on 16097 patients (702 synchronous pmCRC, 15395 non-pmCRC) comparing lymph node metastasis, were included for eligibility in the meta-analysis. The pooled analysis indicated that N1-2 was associated positively with synchronous PM compared with N0 (OR 5.665; 95% CI, 3.628 to 8.848; P < 0.001) (**Fig. 2c**). There was significant heterogeneity (Cochran Q, P = 0.068; I^2 = 62.7 percent). When one study[3] was omitted through sensibility analysis, there was no significant heterogeneity (Cochran Q, P = 0.765; I^2 = 0 percent), with no noticeable influence on the pooled result.

Differentiation

Five studies[15, 17, 25, 41, 43], including data on 108360 patients (21986 synchronous pmCRC, 86374 non-pmCRC) comparing differentiation, were included for eligibility in the meta-analysis. The pooled analysis indicated that poorly differentiated grade was associated positively with synchronous CPM compared with well/moderately differentiated grade (OR 2.560; 95% CI, 1.537 to 4.265; P < 0.001) (**Fig. 2d**). There was significant heterogeneity (Cochran Q, P < 0.001; I^2 = 94.5 percent). When one study[17] was omitted through sensibility analysis, there was no significant heterogeneity (Cochran Q, P = 0.636; I^2 = 0 percent), with no noticeable influence on the pooled result.

Location of primary tumor

Six studies[3, 8, 15, 18, 25, 41] including data on 24331 patients (1610 synchronous pmCRC, 22721 non-pmCRC) regarding right-sided colon cancer were included for eligibility in the meta-analysis. Synchronous

CPM was associated positively with right-sided colon cancer location (OR 2.468; 95% CI, 2.050 to 2.970; P < 0.001) (**Fig. 3a**). There was no significant heterogeneity (Cochran Q, P = 0.119; I^2 = 42.9 percent).

Six studies[3, 8, 15, 18, 25, 41] including data on 24331 patients (1610 synchronous pmCRC, 22721 non-pmCRC) regarding left-sided colon cancer were included for eligibility in the meta-analysis. Synchronous CPM was not associated with left-sided colon cancer location (OR 1.000; 95% CI, 0.761 to 1.314; P = 0.998) (**Fig. 3b**). There was significant heterogeneity (Cochran Q, P = 0.004; I^2 = 71.4 percent). When one study[15] was omitted through sensibility analysis, there was less significant heterogeneity (Cochran Q, P = 0.049; I^2 = 58.0 percent), with no noticeable influence on the pooled result.

Five studies[3, 8, 18, 25, 41] including data on 23278 patients (1519 synchronous pmCRC, 21759 non-pmCRC) regarding rectal cancer were included for eligibility in the meta-analysis. Synchronous CPM was associated negatively with rectal cancer location (OR 0.323; 95% CI, 0.284 to 0.368; P < 0.001) (**Fig. 3c**). There was no significant heterogeneity (Cochran Q, P = 0.969; I^2 = 0 percent).

Histology

Six studies[3, 26, 36, 38, 41, 43] including data on 24252 patients (1600 synchronous pmCRC, 22652 non-pmCRC) regarding non-mucinous adenocarcinoma (NMC) were included for eligibility in the meta-analysis. Synchronous CPM was associated negatively with NMC (OR 0.319; 95% CI, 0.237 to 0.429; P < 0.001) (**Fig. 4a**). There was significant heterogeneity (Cochran Q, P = 0.005; I^2 = 70.4 percent). When one study[36] was omitted through sensibility analysis, there was no significant heterogeneity (Cochran Q, P = 0.106; I^2 = 47.5 percent), with no noticeable influence on the pooled OR and confidence interval.

Seven studies[3, 17, 26, 36, 38, 41, 43] including data on 154377 patients (29448 synchronous pmCRC, 124929 non-pmCRC) regarding mucinous adenocarcinoma (MC) were included for eligibility in the meta-analysis. Synchronous CPM was associated positively with MC (OR 3.565; 95% CI, 2.095 to 6.064; P < 0.001) (**Fig. 4b**). There was significant heterogeneity (Cochran Q, P < 0.001; I^2 = 97.1 percent). In order to explore possible sources of heterogeneity, subgroup analysis was performed. Two studies[17, 36] were divided into the subgroup one that had no significant heterogeneity (Cochran Q, P = 0.228; I^2 = 31.2 percent), with no noticeable influence on the pooled result, and the others[3, 26, 38, 41, 43] were divided into the subgroup two that also had no significant heterogeneity (Cochran Q, P = 0.174; I^2 = 37.0 percent), with no noticeable influence on the pooled result. The subgroup one had much higher OR value in each study than subgroup two.

Three studies[3, 26, 38] including data on 5741 patients (673 synchronous pmCRC, 5068 non-pmCRC) regarding signet-ring cell carcinoma (SRCC) were included for eligibility in the meta-analysis. Synchronous CPM was associated positively with SRCC (OR 4.480; 95% CI, 1.836 to 10.933; P = 0.001) (**Fig. 4c**). There was significant heterogeneity (Cochran Q, P = 0.036; I^2 = 69.7 percent). When one study[3] was omitted through sensibility analysis, there was no significant heterogeneity (Cochran Q, P = 0.656; I^2 = 0 percent), with no noticeable influence on the pooled result. It's noteworthy that the study had a much higher OR value.

Serum CA19-9

Two studies[25, 39], including data on 728 patients (24 synchronous pmCRC, 704 non-pmCRC) regarding serum CA19-9 status, were included for eligibility in the meta-analysis. Serum CA19-9 level of up to 37.0 u/ml was taken as upper cut-off values for reference ranges. Synchronous CPM was associated positively with elevated serum CA19-9 (OR 12.868; 95% CI, 5.196 to 31.867; P < 0.001) (**Fig. 5a**). There was no significant heterogeneity (Cochran Q, P = 0.710; I^2 = 0 percent).

PROK1/PROKR2

Two studies[34, 37], including data on 944 patients (29 synchronous pmCRC, 915 non- pmCRC) regarding PROK1/PROKR2 status, were included for eligibility in the meta-analysis. Synchronous CPM was associated positively with PROK1/PROKR2-positive (OR 2.244; 95% CI, 1.031 to 4.884; P = 0.042) (**Fig. 5b**). There was no significant heterogeneity (Cochran Q, P = 0.344; I^2 = 0 percent).

BRAF status

Nine studies[8, 16, 18, 27-29, 31, 33, 35], including data on 4979 patients (704 synchronous pmCRC, 4275 non-pmCRC) regarding BRAF status, were included for eligibility in the meta-analysis. Synchronous PM was associated positively with BRAF mutations (OR 2.586; 95% CI, 1.674 to 3.994; P < 0.001) (**Fig. 5c**). There was significant heterogeneity (Cochran Q, P = 0.019; I^2 = 56.3 percent). When one study[28] was omitted through sensibility analysis, there was no significant heterogeneity (Cochran Q, P = 0.073; I^2 = 45.9 percent), with no noticeable influence on the pooled OR and confidence interval. It's clearly seen that the study has a smaller sample size.

KRAS status

Six studies[8, 16-18, 28, 33], including data on 134197 patients (28362 synchronous pmCRC, 105835 non-pmCRC) regarding KRAS status, were included for eligibility in the meta-analysis. Synchronous CPM was not associated with KRAS mutations (OR 0.972; 95% CI, 0.576 to 1.638; P = 0.914) (**Fig. 6a**). There was significant heterogeneity (Cochran Q, P < 0.001; I^2 = 92.4 percent). When one study[17] was omitted through sensibility analysis, there was no significant heterogeneity (Cochran Q, P = 0.774; I^2 = 0 percent), with no noticeable influence on the pooled result. It's noteworthy that the rate of KRAS mutations in the synchronous PM group was much lower in the study.

NRAS status

Two studies[16, 28], including data on 731 patients (43 synchronous pmCRC, 688 non- pmCRC) regarding NRAS status, were included for eligibility in the meta-analysis. Synchronous CPM was not associated with NRAS mutations (OR 1.140; 95% CI, 0.133 to 9.748; P = 0.905) (**Fig. 6b**). There was no significant heterogeneity (Cochran Q, P = 0.373; I^2 = 0 percent).

PIK3CA status

Two studies[16, 33], including data on 897 patients (93 synchronous pmCRC, 804 non-pmCRC) regarding PIK3CA status, were included for eligibility in the meta-analysis. Synchronous CPM was not associated with PIK3CA mutations (OR 0.667; 95% CI, 0.289 to 1.540; P = 0.343) (**Fig. 6c**). There was no significant heterogeneity (Cochran Q, P = 0.415; I^2 = 0 percent).

MSI-H/dMMR status

Four studies[16-18, 31], including data on 131015 patients (27922 synchronous pmCRC, 103093 non-pmCRC) regarding MSI-H/dMMR status, were included for eligibility in the meta-analysis. Synchronous CPM was not associated with MSI-H/dMMR (OR 1.087; 95% CI, 0.351 to 3.367; P = 0.885) (**Fig. 6d**). There was significant heterogeneity (Cochran Q, P = 0.097; I^2 = 52.5 percent). When one study[18] was omitted through sensibility analysis, there was no significant heterogeneity (Cochran Q, P = 0.153; I^2 = 46.6 percent), with no noticeable influence on the pooled result.

Publication bias

No significant publication bias was found, according to visual inspection of funnel plot and to Begg's test (supplementary **Fig. S1-S5**).

Discussion

We found that synchronous CPM was associated positively with female, PROK1/PROKR2-positive, right-sided colon cancer location, poorly differentiated grade, BRAF mutations, mucinous adenocarcinoma, signet-ring cell carcinoma, N1-2, T4 and elevated serum CA19-9 (ascendingly sequenced by the value of odds ratios). Our study has provided an extensive analysis of the association between synchronous CPM and clinicopathological-molecular features, especially the molecular characteristics compared with the previously published studies[44-47]. In addition, several studies have different conclusions about the association between MSI-H and synchronous CPM, although MSI-H is a poor prognostic factor in metastatic colorectal cancer[48, 49]. Nonetheless, we found that MSI-H was irrelevant with synchronous CPM in this study. The meta-analytical techniques could increase the volume, which may cause more sufficient statistical power.

Based on the hypothesis that phenotype and the subsequent clinical behavior of CPM is driven by underlying biological mechanisms, readouts of disease biology will contribute to more precise identification of suitable patients and guidance of therapy. This is one of the critical future research targets in CPM. The potential mechanisms of risk factors that associated positively with synchronous CPM are discussed as follows. Due to a longer asymptomatic period, right-sided colon tumors are usually larger in diameter when diagnosed than left-sided colon tumors. Larger neoplasms infiltrate the surface of serosa over a larger area, so it may lead to increased abscission of cancer cells into the peritoneal cavity. In addition, typical genetic differences between right-sided and left-sided colon tumors have been found, such as BRAF status, and these genotypes may bring about a fenotype with a different probability to be associated with synchronous CPM[50]. Several studies have shown that mucinous histologic type

has a poor prognostic impact, including a higher tendency to peritoneal carcinomatosis and a lower efficacy of oxaliplatin and irinotecan-based chemotherapy[51-53]. A more advanced T stage is associated positively with the presentation of peritoneal carcinomatosis, with the potential mechanism that peritoneal carcinomatosis is caused by serosal infiltration of the malignant tumor and subsequent abscission of cancer cells into the peritoneal cavity[54]. Regarding peritoneal tumor spread, CA19-9 was shown to interact with E- and P-selectins expressed on human mesothelial and endothelial cells in the peritoneum[25, 55]. Prokineticin1 (PROK1) is a known ligand of Prokineticin-receptor2 (PROKR2) and transduces important molecular signals to induce physiological changes. The PROK1 protein was identified as a vascular endothelial growth factor. Increased PROK1 expression is associated with angiogenesis involving hematogenous metastasis[34, 37]. Besides direct invasion and hematogenous spread, peritoneal carcinomatosis could be occurred by lymphatic dissemination, which supports the risk factor of N1-2[54, 56, 57].

Some studies once defined the degree of risk of developing colorectal peritoneal carcinomatosis[58, 59]. A high risk of synchronous CPM should modify the management strategy of this special type of metastatic disease, with the following suggestions[5, 58]. First, in CRC patients at high risk of developing synchronous PM, a more aggressive preoperative examination, such as PET-CT, MRI diffusion-weighted and so on, is suggested to be performed to confirm whether there is synchronous PM. Then, if PM is suspected on preoperative imaging, we could propose laparoscopic exploration of the abdominal cavity to assess the extent of the disease and to obtain histological confirmation. Eventually, if the synchronous PM is diagnosed, surgeons are expected to describe the extent of the disease and to determine whether aggressive treatment including complete CRS plus HIPEC should be carried out in patients.

There are some limitations in this study. Firstly, the non-English studies were excluded, with the language bias. Secondly, the risk associated with T4a vs. T4b stage was not analyzed because the specific data was absent in the included studies. Thirdly, factors such as T4 stage and N1-2 stage are of little help, because they can be poorly assessed preoperatively. Finally, the number of included studies about CA19-9, PROK1/PROKR2, NRAS, PIK3CA status is small, which may cause limited statistical power.

Conclusions

To our knowledge, this is the first meta-analysis to reveal the clinicopathological and molecular features of synchronous pmCRC compared to non-pmCRC. These evidence-based predictive factors of synchronous CPM are conducive to enhance the management and select optimal therapeutic strategy.

Abbreviations

PRISMA: Preferred Reporting Items of Systematic Reviews and Meta-analysis; PROSPERO: Prospective Register of Systematic Reviews; N-O score: Score of Newcastle–Ottawa Scale; OR: odds ratios; CI: Confidence interval; CPM: Colorectal peritoneal metastasis; CRC: Colorectal cancer; PM: Peritoneal metastases; pmCRC: Peritoneal metastasis of colorectal cancer; CTGF: Connective tissue growth factor;

DDR2: Discoidindomain receptor 2; VIM: vimentin; NMC: Non-mucinous adenocarcinoma; MC: Mucinous adenocarcinoma; SRCC: Signet-ring cell carcinoma; PROK1: Prokineticin1; PROKR2: Prokineticin-receptor2

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was sponsored by the Guangzhou Science and Technology Plan Project (No. 201704020059). The funding body had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Authors' contributions

H.W designed the study. D.L performed statistical analysis. Y.Z and X.Q wrote, reviewed, and edited the manuscript. Y.D and Z.W performed data interpretation. Y.Z, X.Q, Y.D and H.W performed study selection and data extraction. All authors read and approved the final draft.

Acknowledgements

Not applicable

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Table

Table 1 Characteristics of included studies

Author	Year	Country	Multicentre /unicentre	Study type	Enrollment interval	Number of patient with synchronous PM	Number of patients without synchronous PM	Clinical, pathological and biological characteristics
Sherman et al[17]	2020	USA	M	Retro	2010-2016	27848	102277	Gender, Differentiation, Histology, KRAS, MSI-H/dMMR
Eurboonyanun et al[27]	2020	USA	U	Retro	2004-2018	17	133	BRAF
Cheng et al[29]	2018	Taiwan	U	Retro	2000-2013	76	260	BRAF
Sayagués et al[28]	2018	Spain	U	Retro	-	7	80	BRAF, KRAS, NRAS, TP53
Kaneko et al[25]	2017	Japan	U	Retro	2009-2015	12	383	Gender, Tumor location, T stage, Differentiation, CA19-9, CEA
Jang et al[31]	2017	Korea	U	Retro	2011-2014	30	319	BRAF, MSI-H/dMMR
Sasaki et al[30]	2017	Japan	U	Retro	2009-2014	13	50	DDR2
Franko et al[8]	2016	ARCAD	M	Pro	1997-2008	1371	9169	Gender, Tumor location, BRAF, KRAS
Sasaki et al[33]	2016	Japan	U	Retro	2006-2011	117	409	Gender, BRAF, KRAS, PIK3CA
Huang et al[32]	2016	Taiwan	U	Retro	2000-2010	14	500	CA125
Goi et al[34]	2015	Japan	U	Retro	1990-2007	9	315	PROK1/PROKR2
Cremolini et al[35]	2015	Italy	M	Retro	2006-2014	138	481	BRAF
Shelygin et al[18]	2014	Russia	U	Retro	2012-2014	20	38	Gender, Tumor location, BRAF, KRAS, MSI-H/dMMR
Jimi et al[36]	2014	Japan	U	Retro	1991-2006	29	397	Histology
Nakazawa et al[37]	2014	Japan	U	Retro	1990-2007	20	600	PROK1/PROKR2
Kerscher et al[3]	2013	Germany	U	Pro	1986-2009	115	2150	Tumor location, T stage, LN+, Histology
Smith et al[16]	2013	UK	M	Pro	2003-2005	36	611	BRAF, KRAS, MSI-H/dMMR, NRAS, PIK3CA
Hugen et al[38]	2013	Netherlands	M	Retro	1991-2010	425	1253	Histology
Yu et al[39]	2013	Korea	U	Pro	2008-2011	12	321	CA19-9
Sjo et al[15]	2011	Norway	M	Pro	1993-2006	94	1030	Gender, Tumor location, T stage, LN+, Histology
Lemmens et al[41]	2011	Netherlands	M	Retro	1995-2008	904	17007	Gender, Tumor location, T stage, LN+, Differentiation, Histology
Lin et al[40]	2011	Taiwan	U	Retro	2001-2003	37	99	CTGF
Shirahata et al[42]	2010	Japan	U	Retro	-	5	39	VIM
Song et al[26]	2009	China	U	Retro	1994-2007	149	1857	Histology
Akino et al[43]	2002	Japan	U	Retro	1986-1999	46	610	Histology, Differentiation

M, multicentre; U, unicentre; Retro, retrospective; Pro, prospective; DDR2, discoidindomain receptor 2; PROK1, prokineticin 1; PROKR2, prokineticin receptor 2; CTGF, connective tissue growth factor; VIM, vimentin; LN+, lymph node metastasis.

Figures

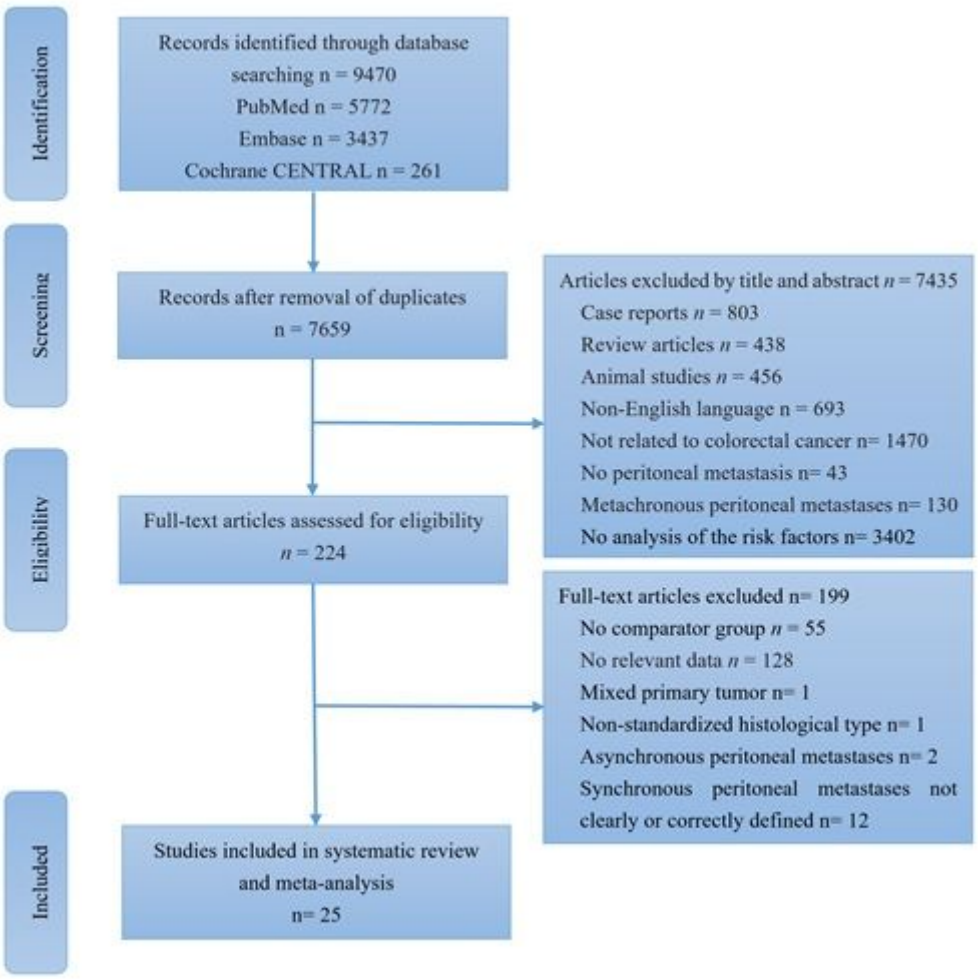

Figure 1

Flow diagram showing search and selection of studies

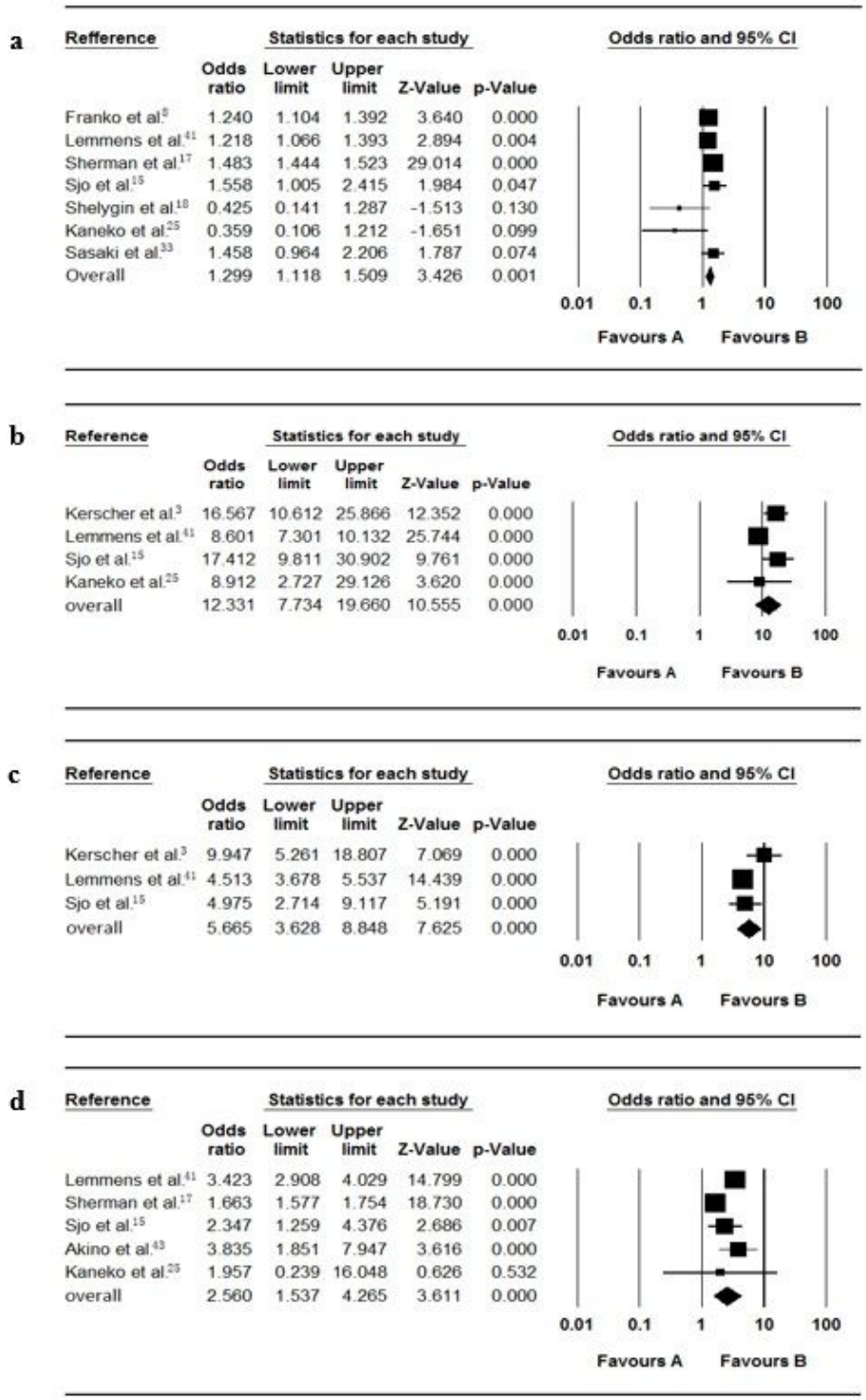

Figure 2

Forest plot for female, T4, N1-2 and poorly differentiated grade. Odds ratios are shown with 95% CI. A, non-pmCRC; B, synchronous pmCRC. a, female (n = 160679; p < 0.001; Cochran Q 25.9, 6 df, p < 0.001; I^2, 76.9). b, T4 (n = 19432; p < 0.001; Cochran Q 11.6, 3 df, p = 0.009; I^2, 74.2). c, N1-2 (n = 16097; p < 0.001; Cochran Q 5.3, 2 df, p = 0.068; I^2, 62.7). d, poorly differentiated grade (n = 108360; p < 0.001; Cochran Q 73.0, 4 df, p < 0.001; I^2, 94.5).

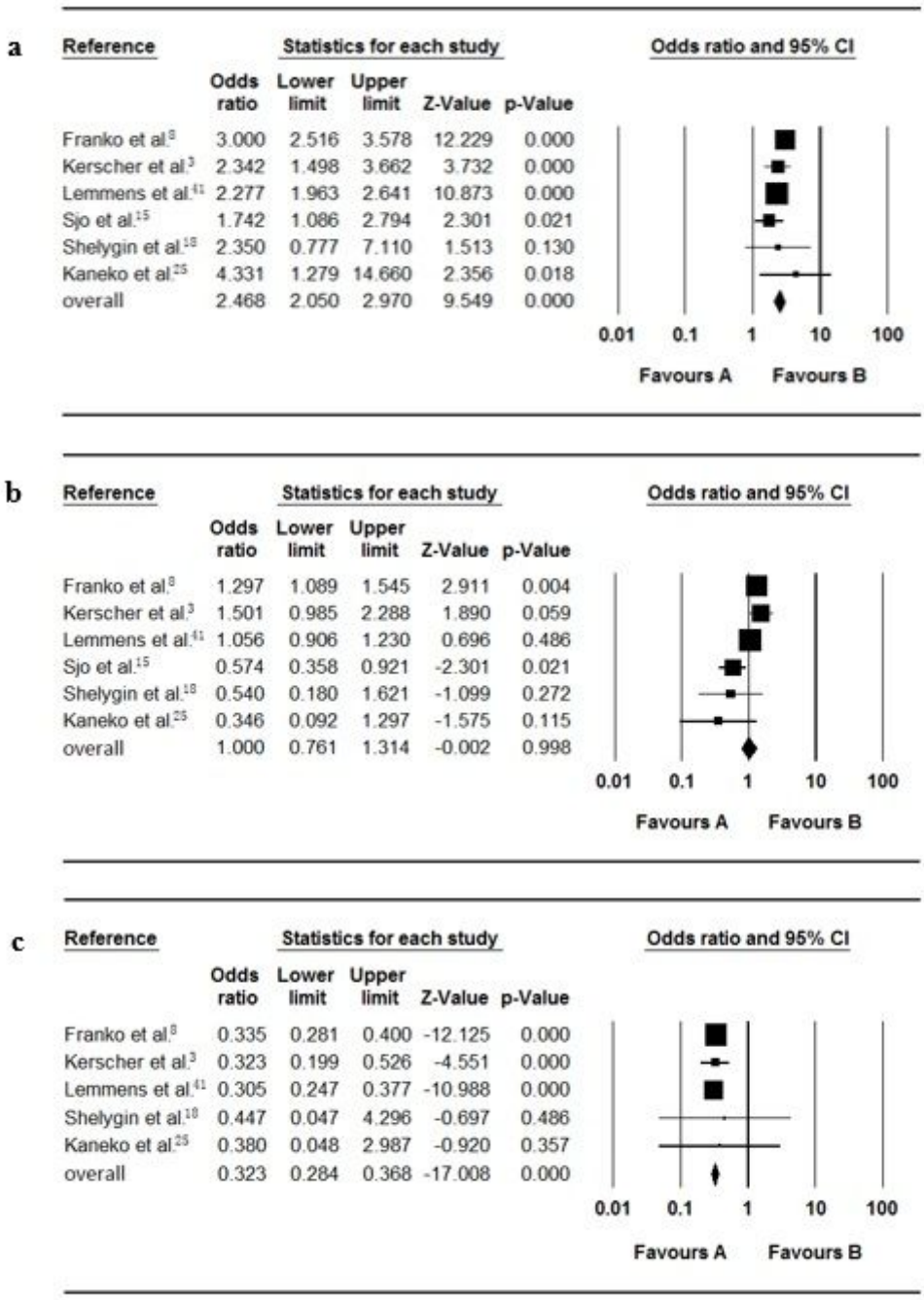

Figure 3

Forest plot for right-sided colon, left-sided colon and rectum. Odds ratios are shown with 95% CI. A, non-pmCRC; B, synchronous pmCRC. a, right-sided colon (n = 24331; p < 0.001; Cochran Q 8.7, 5 df, p = 0.119; I^2, 42.9). b, left-sided colon (n = 24331; p = 0.998; Cochran Q 17.5, 5 df, p = 0.004; I^2, 71.4). c, rectum (n = 23278; p < 0.001; Cochran Q 0.5, 4 df, p = 0.969; I^2, 0).

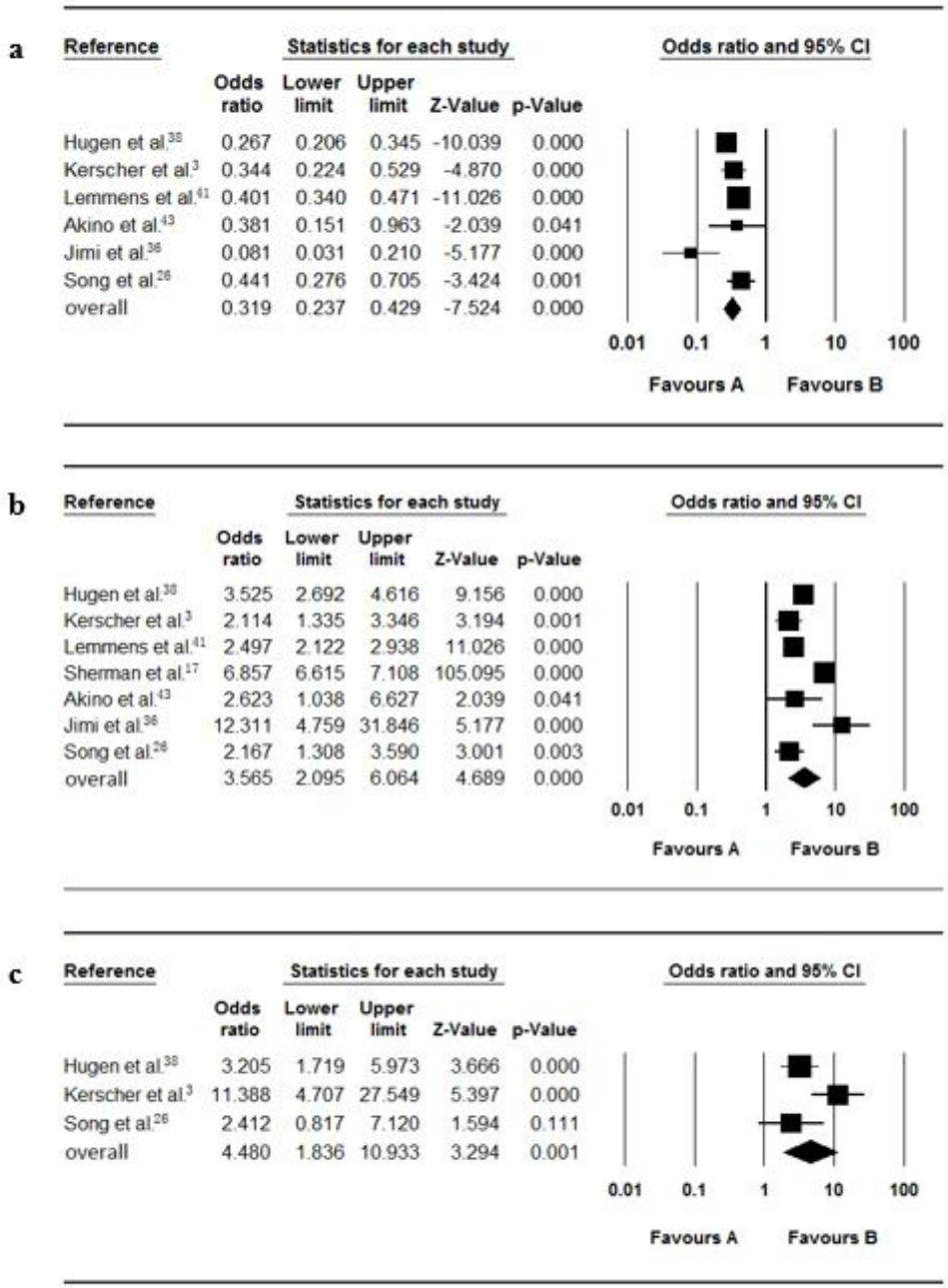

Figure 4

Forest plot for non-mucinous adenocarcinoma (NMC), mucinous adenocarcinoma (MC) and signet-ring cell carcinoma (SRCC). Odds ratios are shown with 95% CI. A, non-pmCRC; B, synchronous pmCRC. a, NMC (n = 24252; p < 0.001; Cochran Q 16.9, 5 df, p = 0.005; I^2, 70.4). b, MC (n = 154377; p = 0.998; Cochran Q 207.0, 6 df, p < 0.001; I^2, 97.1). c, SRCC (n = 5741; p = 0.001; Cochran Q 6.6, 2 df, p = 0.036; I^2, 69.7).

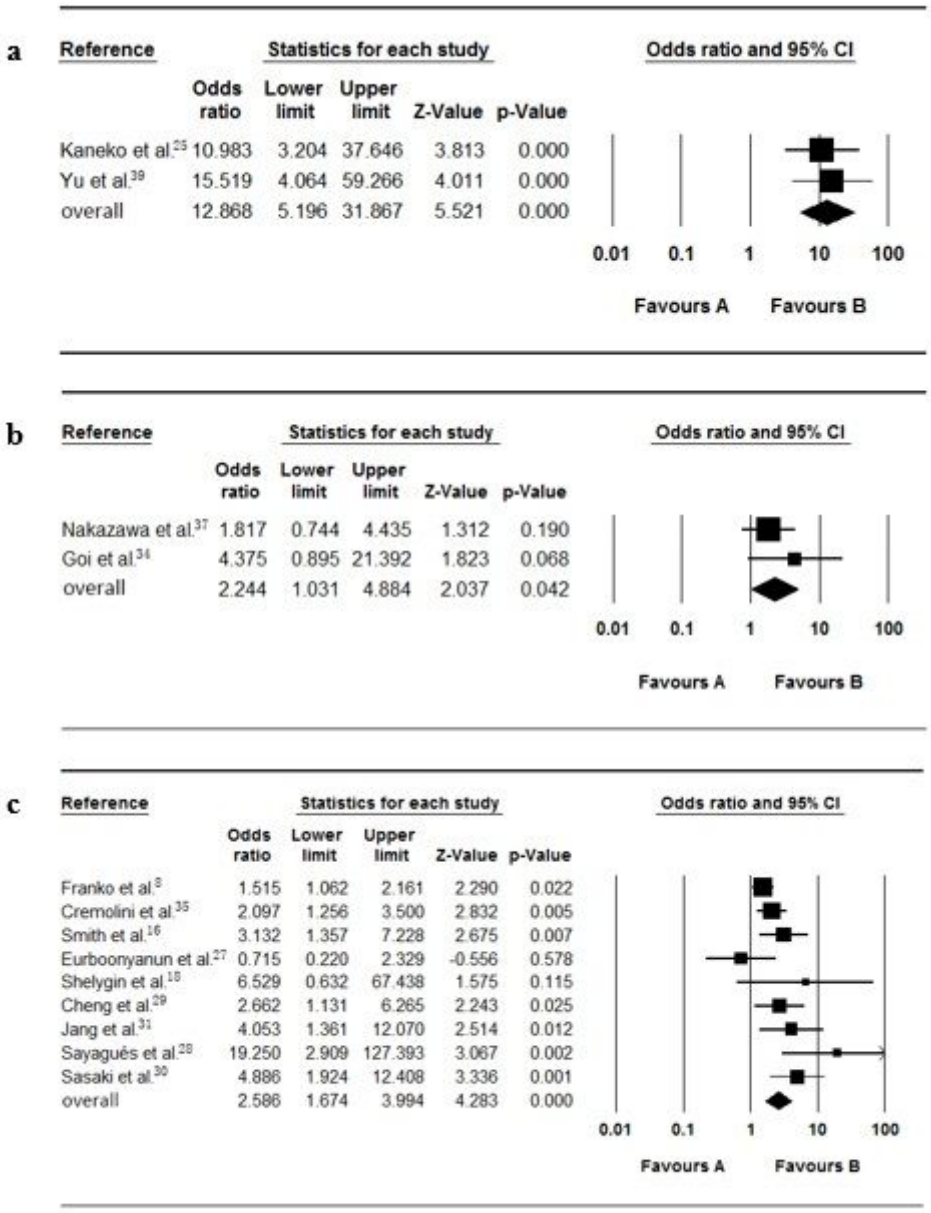

Figure 5

Forest plot for serum CA19-9, PROK1/PROKR2 and BRAF. Odds ratios are shown with 95% CI. A, non-pmCRC; B, synchronous pmCRC. a, serum CA19-9 (n = 728; $p < 0.001$; Cochran Q 0.1, 1 df, $p = 0.710$; I^2, 0). b, PROK1/PROKR2 (n = 944; $p = 0.042$; Cochran Q 0.8, 1 df, $p = 0.344$; I^2, 0). c, BRAF (n = 4979; $p < 0.001$; Cochran Q 18.3, 8 df, $p = 0.019$; I^2, 56.3).

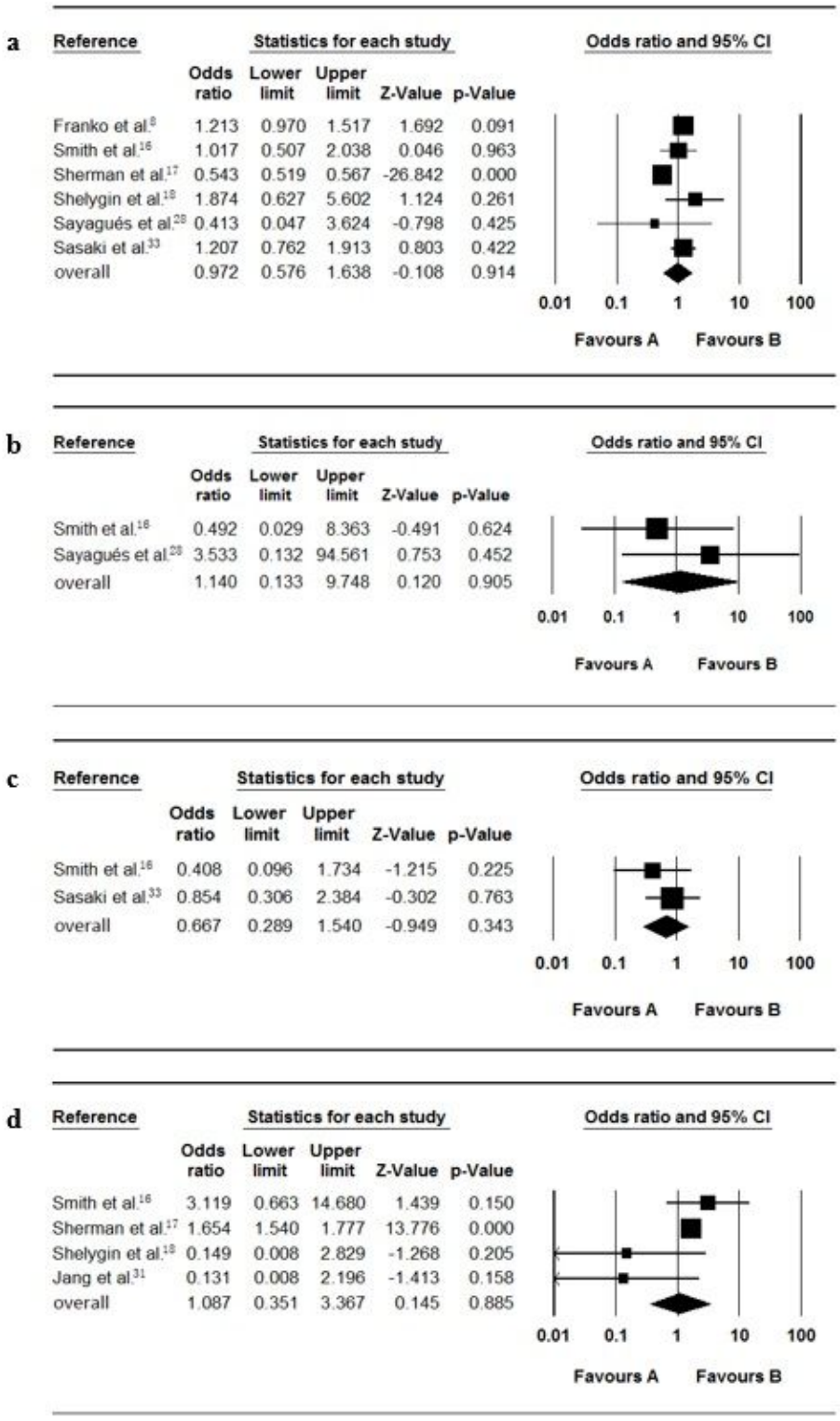

Figure 6

Forest plot for KRAS, NRAS, PIK3CA and MSI-H/dMMR. Odds ratios are shown with 95% CI. A, non-pmCRC; B, synchronous pmCRC. a, KRAS (n = 134197; p = 0.914; Cochran Q 65.8, 5 df, p < 0.001; I^2, 92.4). b, NRAS (n = 731; p = 0.905; Cochran Q 0.7, 1 df, p = 0.373; I^2, 0). c, PIK3CA (n = 897; p = 0.343; Cochran Q 0.6, 1 df, p = 0.415; I^2, 0). d, MSI-H/dMMR (n = 131015; p = 0.885; Cochran Q 6.3, 3 df, p = 0.097; I^2, 52.5).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFig.S1S5.docx
- SupplementaryAppendix1.doc